sensitizing EGFR mutations.[1] Possible explanations for the noncross resistance of EGFR tyrosine kinase to gefitinib and erlotinib include a true qualitative difference between the two molecules, differential sensitivity of gefitinib and erlotinib to known acquired secondary mutations like T790M possibly conferred by other unknown mutations,[4] or yet unknown mechanisms of acquired resistance which may entail nonoverlapping susceptibilities of gefitinib and erlotinib. The clinical benefit seen with the readministration of gefitinib in our patient could also be explained by the loss of acquired-resistance after a significant "TKI-free interval".[2] Conventional chemotherapy given during the TKI-free interval could also have resulted in reduction of TKI-resistant clones, leaving TKI-sensitive ones susceptible to subsequent rechallenge with the same drug.[2]

Applying the principles of clinical noncross resistance between gefitinib and erlotinib,[1,3–5] as well as the loss of acquired-resistance after a TKI-free interval,[2] we obtained repeated responses and a prolonged survival in this patient by an unprecedented alternating use of gefitinib and erlotinib.

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Alvin S. Wong, MD
Department of Hematology Oncology

Kar-Yin Seto, MD
Department of Diagnostic Imaging

Tan-Min Chin, MD
Ross A. Soo, MD
Department of Hematology Oncology
National University Hospital
Singapore

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Docetaxel as Second Line Therapy in Advanced Non-small Cell Lung Cancer—The Dose and Combination May Matter!

To the Editor:

We read with interest the study by Sekine and coworkers[1] wherein the authors have assessed the efficacy of docetaxel as second line therapy in advanced nonsmall cell lung cancer (NSCLC). This study, reinforces the usefulness of docetaxel monotherapy after failure of first line chemotherapy in advanced NSCLC. There are certain issues related to the current study, however, which need further clarification.

Firstly, docetaxel was administered at the dose of 60 mg/m^2 every 3 weeks leading to a dose intensity of 20 mg/m^2/wk. Previous randomized trials that have assessed the efficacy of docetaxel as second line therapy in NSCLC have used dose regimens of either 100 mg/m^2 or 75 mg/m^2 every 3 weeks which have thus meant dose intensities of 33 and 25 mg/m^2/wk, respectively.[2–5] The use of docetaxel at dose of 100 mg/m^2 was associated with significant hematological and nonhematological toxicity whereas its usage at 75 mg/m^2 was well tolerated. Infact, even in other solid tumors, wherein docetaxel has been administered as 3 weekly cycles, the dose that has been most frequently used and is currently recommended has been 75 mg/m^2.[6]

Secondly, statistically significant differences existed between the paclitaxel (P) and nonpaclitaxel (NP) groups with respect to the percentage of patients with stage III disease (26.8 versus 51.0%; $p = 0.002$) and the percentage of patients who had received radiation therapy (0 versus 29.0%; $p < 0.001$).

Moreover, an individual patient data meta-analysis involving 2968 patients from nine randomized trials has shown that the objective response rates are higher for patients treated with cisplatin than for those treated with carboplatin [30 versus 24%; odds ratio {OR} = 1.37, 95% confidence interval {CI} = 1.16–1.61; $p < 0.001$].[7] Infact, carboplatin-based chemotherapy was associated with a statistically significant increase in mortality among patients with nonsquamous histology (hazards ratio = 1.12; 95% CI = 1.01–1.23) and among those treated with third generation chemotherapeutic agents (docetaxel, paclitaxel and gemcitabine) (hazards ratio = 1.11; 95% CI = 1.01–1.21). On the other hand, cisplatin-based chemotherapy is associated with a higher incidence of grade 3/4 nausea and vomiting and nephrotoxicity (OR = 0.39; 95% CI = 0.30–0.52; $p < 0.00001$ and OR = 0.31; 95%CI, 0.17–0.56; $p = 0.0001$).[8] In the current study, cisplatin had been administered in 72% of patients in the NP group whereas all the patients in the P group had received carboplatin.

It is therefore possible that use of a lesser dose intensity of docetaxel, inherent differences in the efficacy and toxicity profile of individual platinum compounds as well as differences in the baseline characteristics of patients in the P and NP groups could have acted as potentially confounding factors in the current study. These factors could have

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Address for correspondence: Navneet Singh, MD, DM (Pulmonary Medicine and Critical Care), FCCP, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Sector 12, Chandigarh 160012, India. E-mail: navneetchd@yahoo.com

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thus influenced the results including those assessed (overall survival) and not assessed (disease free survival and time to progression). Future studies on the efficacy of docetaxel as a second line agent should serve to address issues like the optimal dose regimen and intensity as well as adjust for potential confounders.

Navneet Singh, MD, DM, FCCP
Ashutosh N. Aggarwal, MD, DM, FCCP
Department of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research (PGIMER)
Chandigarh
India

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Reply: Higher Intensity Does Not Necessary Yield Better Survival in Second-Line Chemotherapy for NSCLC

To the Editor:

We would like to thank Singh et al. for suggesting that the dose of docetaxel and previous treatment modality may have an impact on second-line therapy in non-small cell lung cancer (NSCLC). Herein, we discuss the dose of docetaxel and the influence of previous chemotherapy in relation to second-line treatment of NSCLC.

In second-line chemotherapy for NSCLC, whether a higher dose of an anticancer agent would inevitably yield a longer survival is open to question. In a study comparing docetaxel 100 mg/m^2, docetaxel 75 mg/m^2 and best supportive care, the overall survivals were 5.9, 7.5, and 7.0 months, respectively.[1] Docetaxel 100 mg/m^2 was also found to be inferior to docetaxel 75 mg/m^2 in terms of the 1-year survival rate in another phase III study.[2] A similar tendency was also observed for another agent in the second-line setting; pemetrexed 500 mg/m^2 and 900 mg/m^2 were compared, and the overall median survivals were 6.7 and 6.9 months, respectively, and the hazard ratio was 1.013 (95% confidence interval, 0.837–1.226).[3] Even the response rate in the 900 mg/m^2 arm did not exceed that in the 500 mg/m^2. Thus, finding the optimal dose of docetaxel or other agents for second-line chemotherapy may be an intriguing issue.[4]

Meanwhile, docetaxel 60 mg/m^2 is the standard therapeutic dose in Japan, since a Japanese phase I trial determined the maximum tolerated dose to be 70 mg/m^2.[5] Even though this dose of docetaxel is lesser than that used in other countries, this may be the optimal dose for Japanese. In a phase II study of docetaxel for previously untreated NSCLC conducted in Japan, the response rate to docetaxel 60 mg/m^2 was 19%, no less than that to the higher doses used in other countries.[6] A retrospective study evaluating docetaxel 60 mg/m^2 for previously treated NSCLC also showed a response rate of 18.5%, comparable with that reported for higher doses.[7] This difference in the dose requirement in Japanese may be attributed to ethnic differences between the Japanese and other populations, but the issue remains under debate.

The previously employed treatment modality differed between those who had received a combination of carboplatin and paclitaxel (group P) and those who had received a combination of a platinum and an agent other than paclitaxel [group nonpaclitaxel (NP)] in our study. We consider, however, that this difference had only a small impact on our study results, for three reasons. Firstly, all the patients in our study had metastatic disease at the time of recurrence and start of docetaxel therapy. Secondly, although 29% of patients in group NP had received radiotherapy, the response rate to the previous treatment in group NP was the same as that in group P (45.0 versus 44.9%, respectively). In general, the response rate to chemoradiotherapy is higher than that to chemotherapy alone. This difference may have disappeared in our study, probably because we only recruited patients who developed recurrence after chemoradiotherapy. Finally, no previous studies of second-line chemotherapy for NSCLC have dealt with these issues. Even though multiple modalities may have been used in previous treatment, we can only evaluate the integrated result of the treatment. It is impossible to distinguish between the efficacy of chemotherapy and radiotherapy if both are undertaken simultaneously.

In conclusion, further investigation of the optimal dose of chemotherapeutic agents for second-line chemotherapy of NSCLC is warranted. The efficacy of previous chemotherapy, whether or not administered in combination with radiotherapy, is a useful reference for subsequent docetaxel therapy.

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Address for correspondence: Ikuo Sekine, MD, PhD, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1–1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: isekine@ncc.go.jp

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